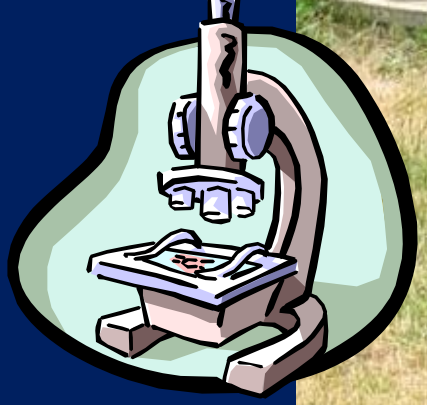
NOPHO

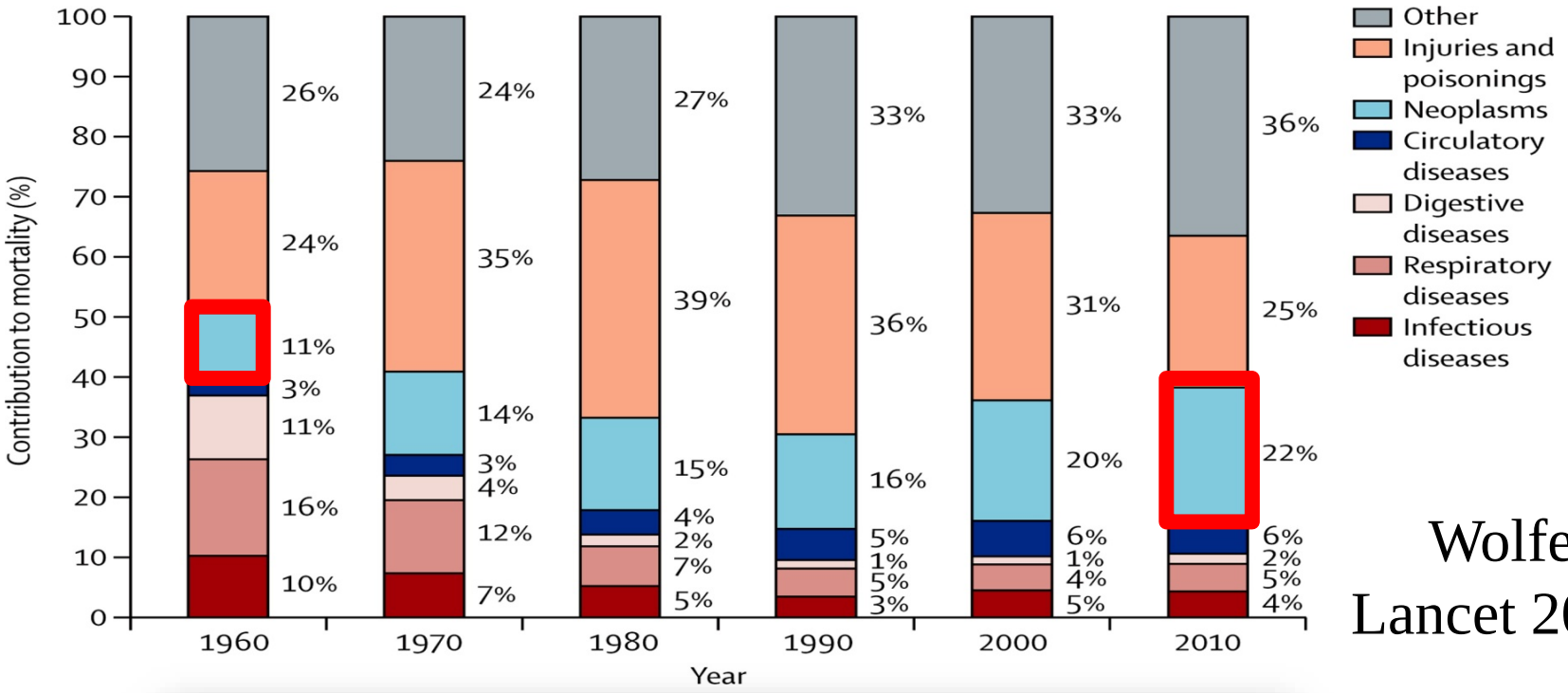


Nordic clinical trials and registries in a pediatric oncology setting

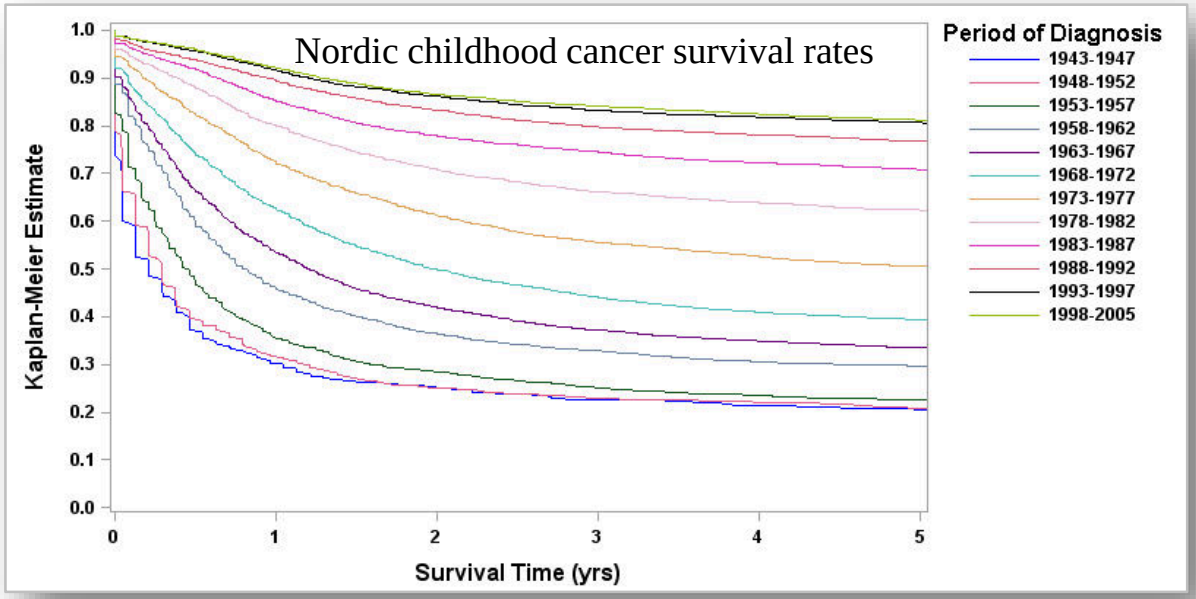
Kjeld Schmiegelow
Professor
Pediatrics & Pediatric Oncology
Rigshospitalet, Copenhagen

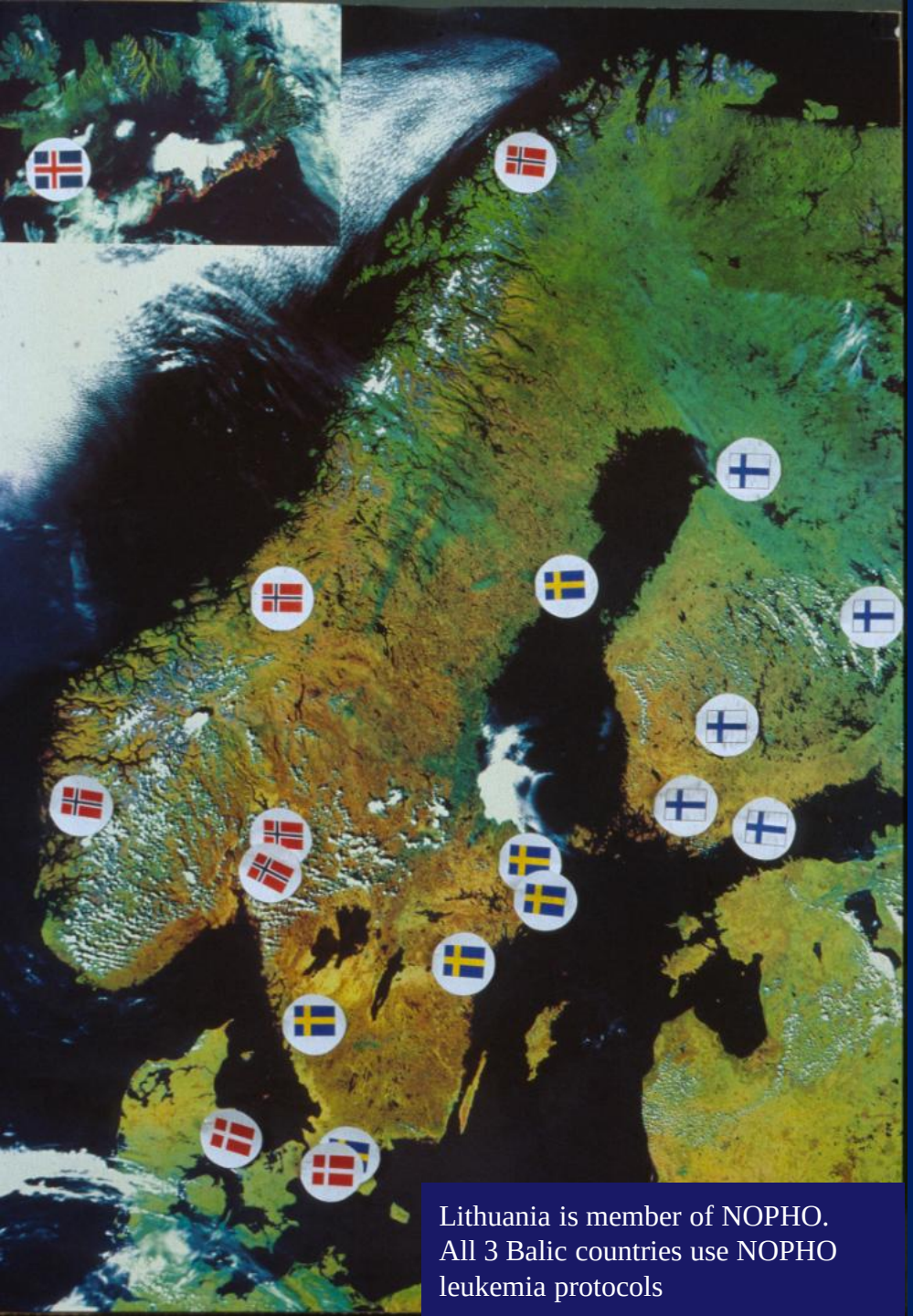
February 19th 2018

Childhood mortality in Europe (1.0-14.9 years)



Wolfe
Lancet 2013





Lithuania is member of NOPHO.
All 3 Balic countries use NOPHO leukemia protocols

NOPHO

6 Countries, 6 languages

Population 25 millions
5 million children

200 with ALL per year

30+ ALL treatment centres

Common NOPHO protocols since 1986

Finding the genomic pieces

Patient trajectory & domains of research

Etiology	Tumor biology	Therapy	Pharmacology	Phase 1&2 therapy	Toxicities	Efficacy Cure	Late effects Rehabilitation
Host genome	Tumor genome	Tumor genome	Host genome	Tumor genome	Host genome	Tumor & host genomes	Host genome

Nordic pediatric clinical research:

- Tumor biology (leukemia biobank; Uppsala)
- Dynamics of biomarkers (cytokines; pharmacology vs clinical outcome (residual leukemia; relapse; death in remission; second cancers)
- Clinical interventions: Observational (non-Rx) & Rx studies
- 1st NOPHO randomised study 1992 – pharmacology of maintenance therapy: 538 pts (97% of all eligible); 10,000 samples; 30,000 treatment data sets; >20 publications

Schmiegelow, since 2009:

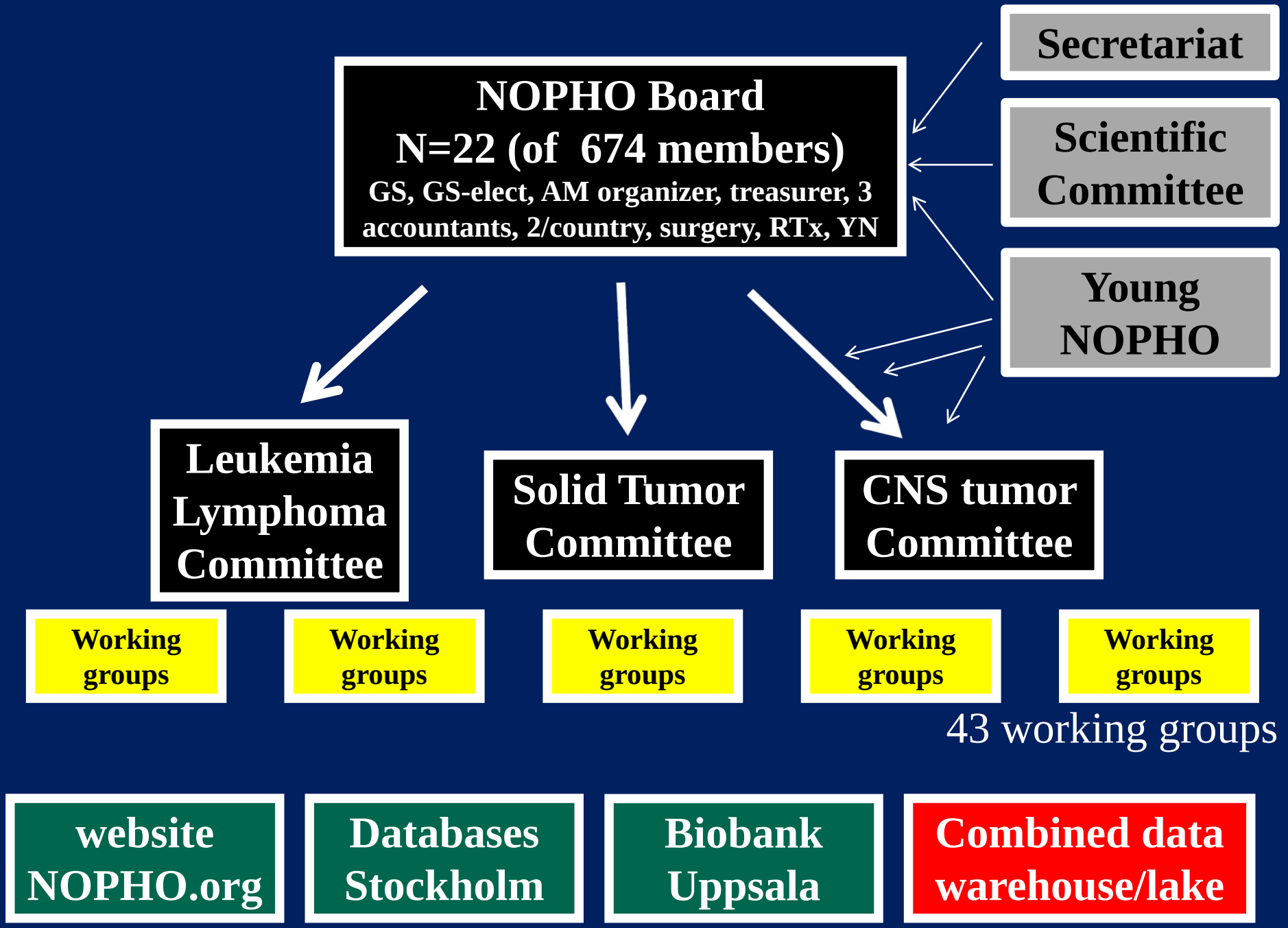
173 publications

50% Nordic;

+6% potentially (DK register studies)

NCU supported studies:

Epidemiology, pharmacology, tumor biology, clinical interventions (+/- Rx), outcome


Secretariat
NOPHO Board
N=22 (of 674 members)
GS, GS-elect, AM organizer, treasurer, 3 accountants, 2/country, surgery, RTx, YN
Scientific Committee
Young NOPHO
Leukemia Lymphoma Committee
Solid Tumor Committee
CNS tumor Committee
Working groups
Working groups
Working groups
Working groups
Working groups
43 working groups
website NOPHO.org
Databases Stockholm
Biobank Uppsala
Combined data warehouse/lake

Acute Lymphoblastic Leukemia 25% of all pediatric cancers

- Rare disease
- Little interest of the pharma industry
  - Except immunotherapy
- Purely investigator-initiated/-driven research
  - Central Database
  - Biobank
  - Nordic prospective trials / studies

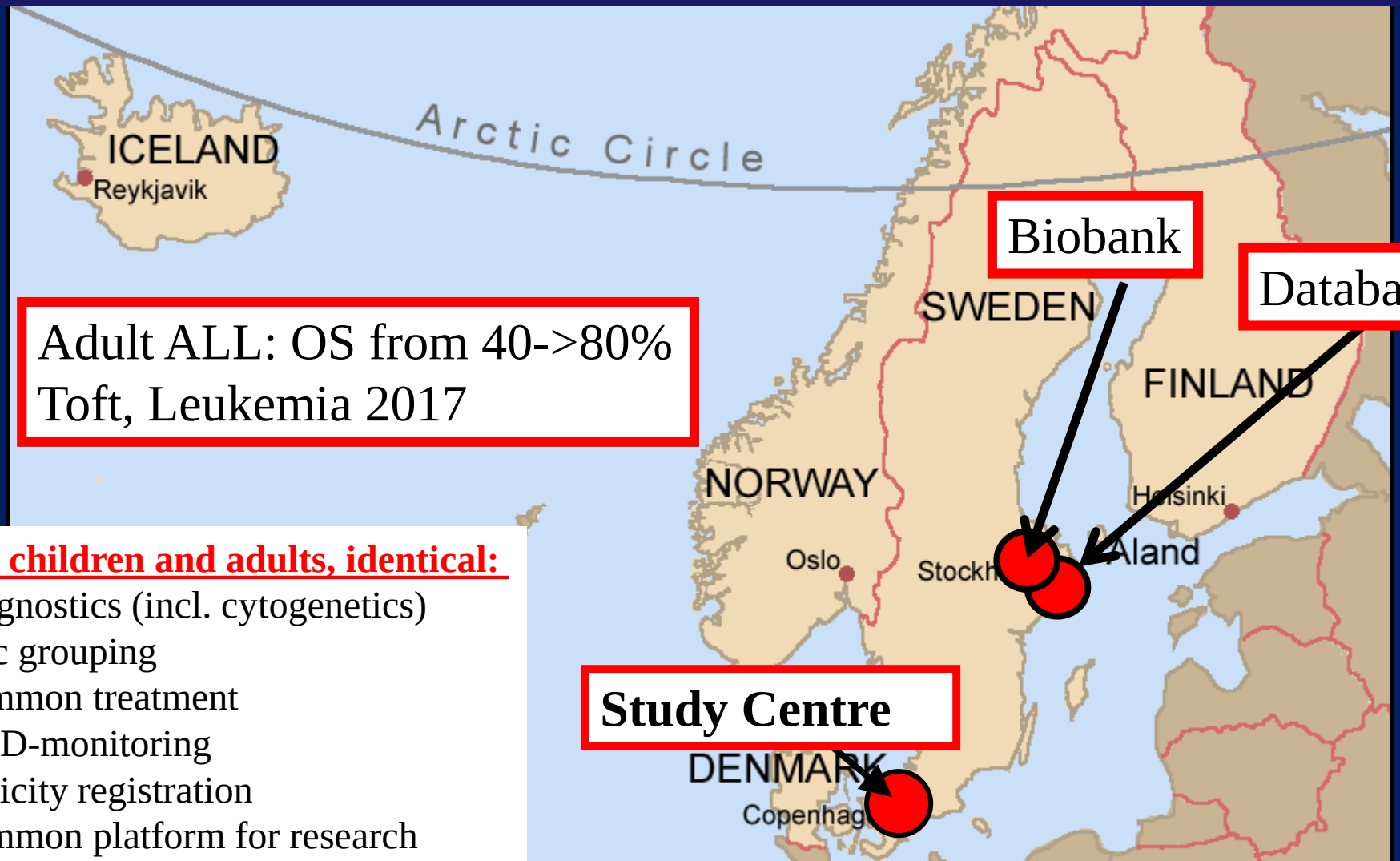
Nordic Clinical ALL Trial Challenges

- 5 (7) countries, 5 (7) languages
- 5 (7) national authorities – Medicines Agencies
- 5 (7) National Data protection agencies
- 5 (7) Ethical Boards
- 5 (7) interpretations of the EU Directive and 5 (7) sets of ethical rules
- Strategy and funding for GCP monitoring in Investigator Initiated trials

NOPHO ALL-2008

Accrual goal (2008-2016):

1700 children	**1.0-18 Years**	**5 Nordic countries (+Rx)**
400 children	**1.0-18 Years**	**2 Baltic countries (-Rx)**
300 adults	**18-45 Years**	**DK, S, N, LT, EE (+SF 2016) (-Rx)**



Adult ALL: OS from 40->80%
Toft, Leukemia 2017

For children and adults, identical:

Diagnostics (incl. cytogenetics)
Risc grouping
Common treatment
MRD-monitoring
Toxicity registration
Common platform for research

Strategy of monitoring and registration

Biggest challenge in the Nordic Pediatric Oncology setting: Ethical applications – not registries

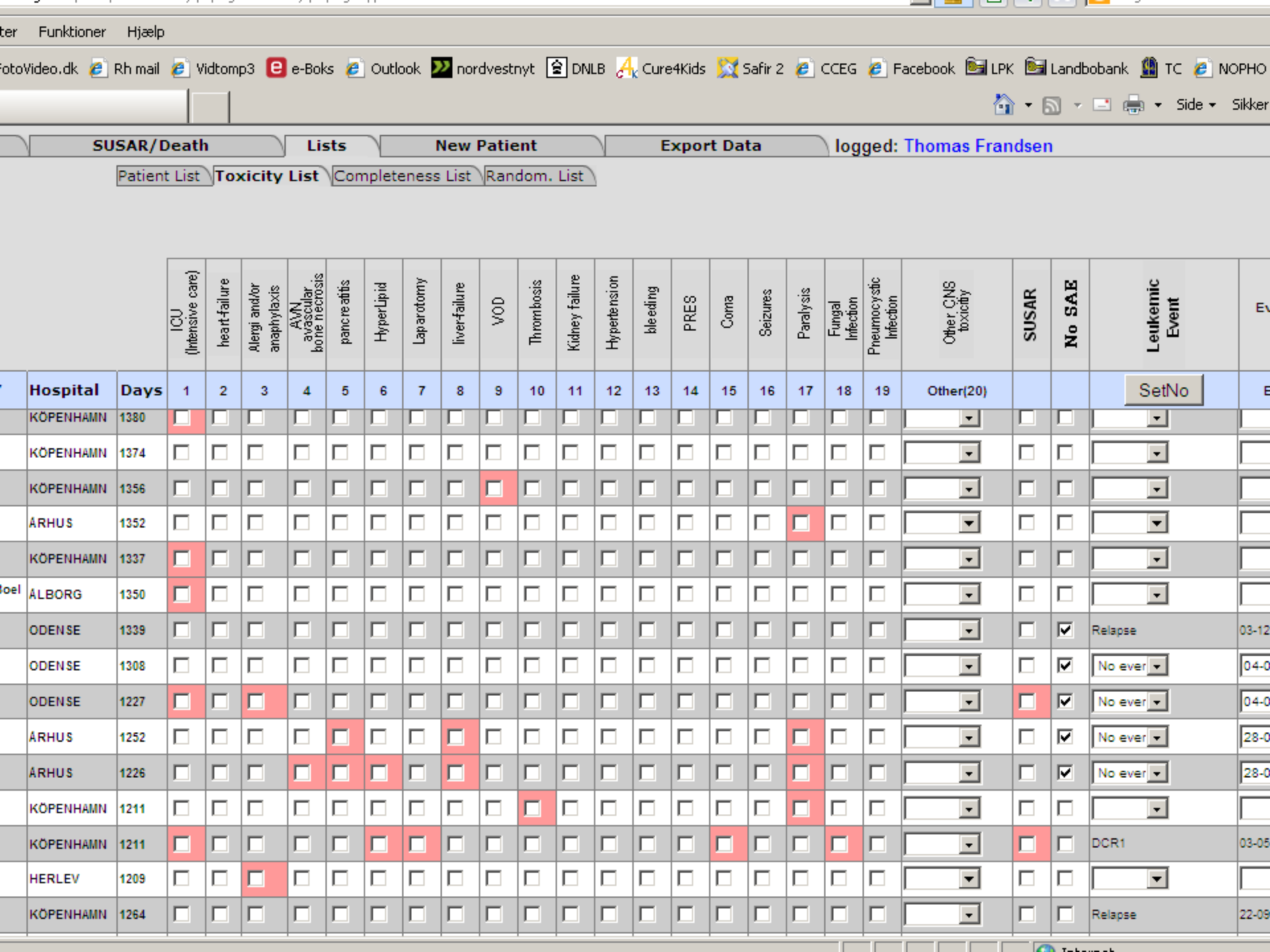
- One entry

Or perhaps

- VHP- like ethical application

Strategy for the trial

- **Simple, on-line dataregistration, including SAEs, Death and SUSAR's**
- **Exclusion of known AE's**
- **Continuous monitoring of entered data by the study centre. Errors are picked up within a short period.**
- **Nordic GCP network**
- **Help-desk**


ter Funktioner Hjælp
FotoVideo.dk Rh mail Vidtomp3 e-Boks Outlook nordvestnyt DNLB Cure4Kids Safir 2 CCEG Facebook LPK Landbobank TC NOPHO
Side Sikker
SUSAR/Death
Lists
New Patient
Export Data
logged: Thomas Frandsen
Patient List
Toxicity List
Completeness List
Random. List
ICU (Intensive care)
heart-failure
Allergi and/or anaphylaxis
AVN avascular bone necrosis
pancreatitis
HyperLipid
Laparotomy
liver-failure
VOD
Thrombosis
Kidney failure
Hypertension
bleeding
PRES
Coma
Seizures
Paralysis
Fungal Infection
Pneumocystic Infection
Other CNS toxicity
SUSAR
No SAE
Leukemic Event
Hospital
Days
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
Other(20)
SetNo
KØPENHAMN 1380
KØPENHAMN 1374
KØPENHAMN 1356
ÅRHUS 1352
KØPENHAMN 1337
ALBORG 1350
ODENSE 1339 Relapse 03-12
ODENSE 1308 No ever 04-0
ODENSE 1227 No ever 04-0
ÅRHUS 1252 No ever 28-0
ÅRHUS 1226 No ever 28-0
KØPENHAMN 1211
KØPENHAMN 1211 DCR1 03-05
HERLEV 1209
KØPENHAMN 1264 Relapse 22-09

Strategy for the trial

- Simple, on-line dataregistration, including SAEs
- Exclusion of known AE's
- Continuous monitoring of registered data by the study centre. Errors are picked up within a short period.
- Nordic GCP network
- Help-desk

AEs not to be reported

- **a number of toxicities are so well-known and frequent during therapy that they will not be reported. These includes:**
- **For the 6MP increment study, the following will not be AE-reported:**

- ❖ Since **leukopenia** is the target toxicity (monitoring parameter), this side-effect will not be regarded as a SAE. This also includes febrile neutropenia leading to hospitalisation or prolongation of ongoing hospitalisation if the patients condition otherwise is good with no signs of septic shock.
- ❖ Since **thrombocytopenia** is the target toxicity (monitoring parameter) this side-effect will not be regarded as a SAE.
- ❖ **A rise in aminotransferases** with normal liver function tests (i.e. bilirubin and INR (or coagulation factor 2-7-10) is a well-known side effect of HD-MTX and 6MP and will not be regarded as a SAE, unless in combination with 19.3.1.8.
- ❖ **A rise in bilirubin** to less than 5x UNL.
- ❖ A **fall in coagulation factors**, unless in combination with 19.3.1.8.
- ❖ Less than a grade 4 rise in amylase (>5x UNL, if measured) will not be reported.
- ❖ **Kidney dysfunction** is a well-known side effect of HD-MTX and will not be regarded as SAE unless it requires dialysis or leads to a permanent kidney dysfunction with s-creatinine >UNL.
- ❖ **Stomatitis and dyspepsia** with or without liver toxicity are a well-known side effects of HD-MTX and will not be regarded as SAE.
- ❖ **Infection/fever** leading to hospitalisation or prolongation of existing hospitalisation.

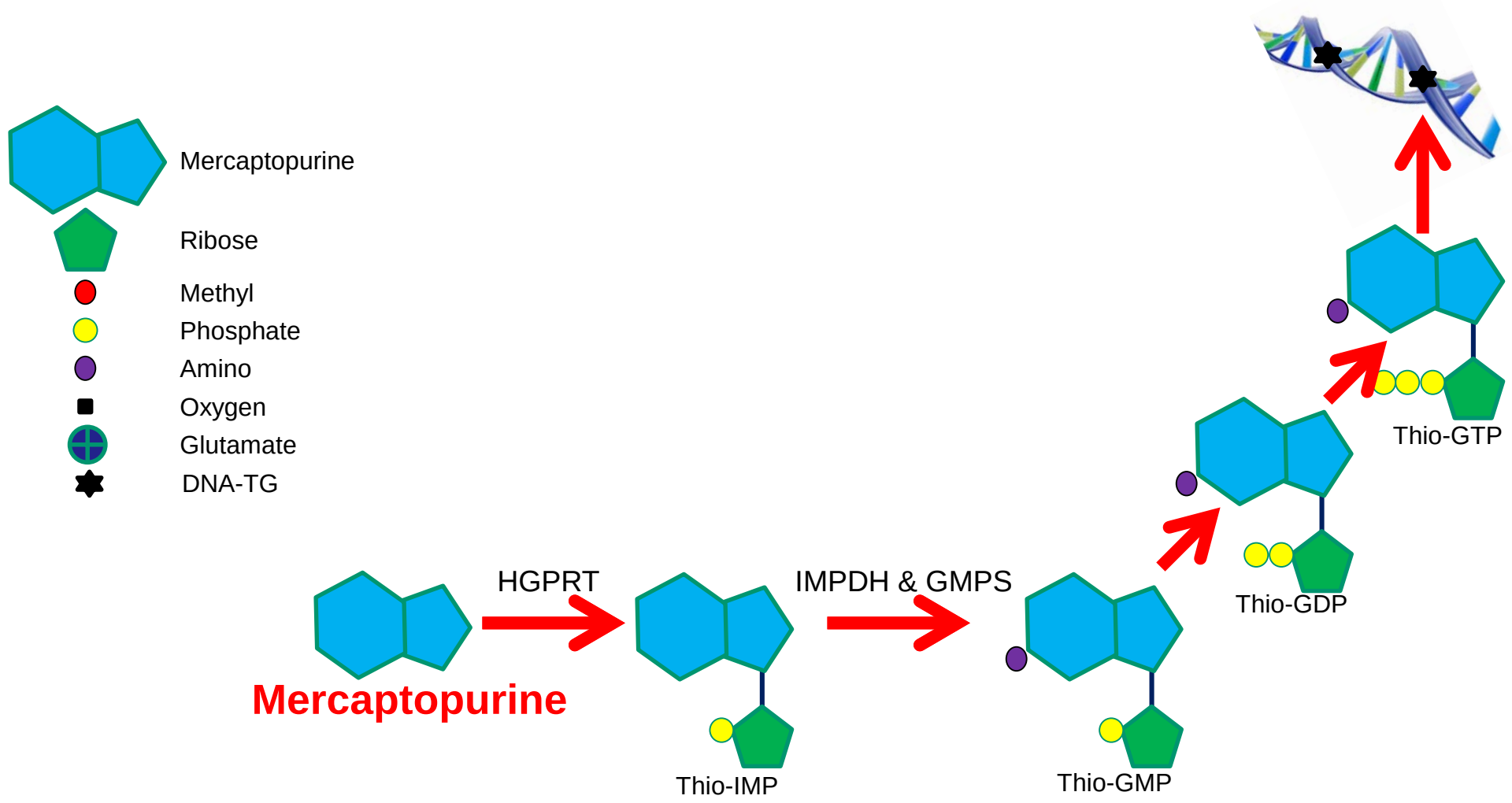
Compliance

- **<u>Quarterly registrations:</u> 33 out of 34 centres (97%) register within 1 months (both adult and child centers)**
- **> 99 % of eligible patients participate in the common treatment protocol (2½ years)**
- **80-85% participate in randomizations**

Acute Lymphoblastic Leukemia
25% of all pediatric cancers

- **Rare disease**
- **Little focus from the pharma industry**
- **Purely investigator-initiated/-driven research**
  - **Central Database**
  - **Biobank**
  - **Nordic prospective trials / studies**
- **From 2019: NOPHO →**

  ALLtogether (14 European countries)



Schmiegelow et al. JPHO 2014 (review)

NOPHO ALL2008 Maintenance therapy study

- 1016 non-HR ALL patients were eligible
  - 7 no family consent
  - 101 no samples taken
- 918 included (89% of all eligible)
  - 526 MRD-positive day 29
  - 390 MRD-negative day 29
  - 2 no MRD status
- 5y-EFS: 92.4% (40 relapses)
- Standard risk (N=549; 60%)
  - BCP with MRD <0.1% day 29
  - No CNS3
  - No i21amp
  - No t(1;19)
  - No dic(9;10)

	Patients (n=918)
Age at diagnosis (years)	4·2 (2·9–7·3)
Sex	
Male	489 (53%)
Female	429 (47%)
White blood cell count at diagnosis (×10⁹ cells per L)	9·2 (4·3–30·9)
Risk group	
Standard	549 (60%)
Intermediate	369 (40%)
Immunophenotype	
B-precursor leukaemia	854 (93%)
T-cell leukaemia	64 (7%)

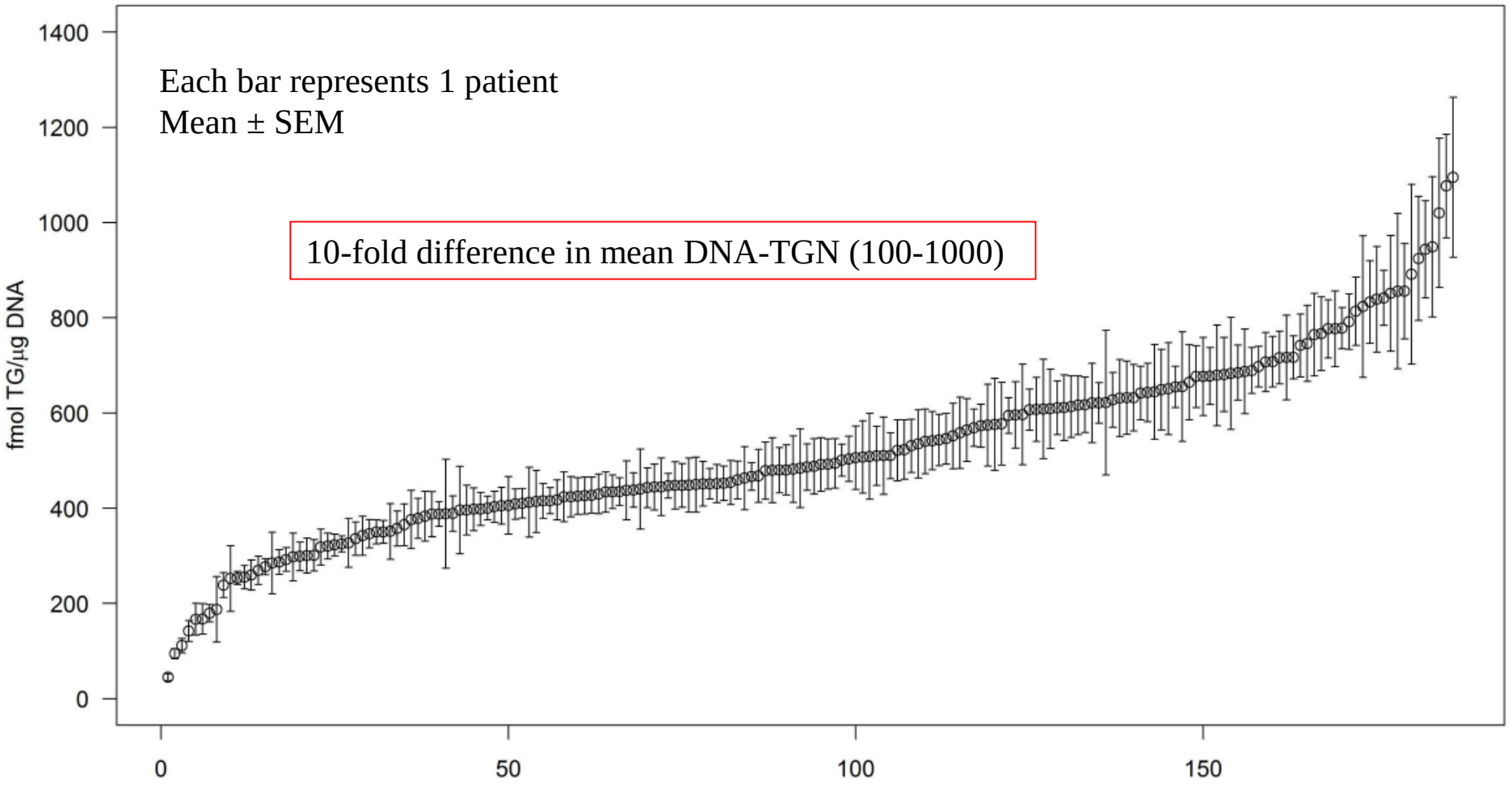
Data are n (%) or median (IQR).

- 346 in CR1 at end of therapy & >5 samples in 6MP/MTX maintenance
  - Pharmacological modelling

Nielsen, Lancet Oncol 2017

186 patients with ≥10 DNA-TGN measurements during last 1.5 years of maintenance
NOPHO ALL2008 maintenance therapy study

Patients can be classified according to their DNA-TGN



Individidual patients; all had completed therapy and and were in CR1 at follow-up

Nielsen, Lancet Oncol 2017

Risk of relapse by DNA-TGN
NOPHO ALL-2008 918 non-HR patients reaching start of maintenance therapy
Measurements per patient (in MT-2, only 6MP/MTX); median N=9 (1-56)
>10,000 blood samples

	Positive MRD day 29 n = 526, 31 relapses			**Negative MRD day 29 n = 390, 9 relapses**		
	Relapse specific HR	95% CI	p-value	Relapse specific HR	95% CI	p-value
DNA-TGN per 100[a]	**0.723**	0.572–0.913	**0.0065**	1.010	0.733–1.391	0.95
Age at diagnosis	1.118	1.037–1.205	**0.0035**	1.073	0.923–1.247	0.36
Female sex	1.036	0.511–2.100	0.92	0.613	0.149–2.524	0.49
WBC at Dx per $10x10^9$/L	1.001	0.998–1.005	0.56	1.005	1.007–1.097	**0.022**

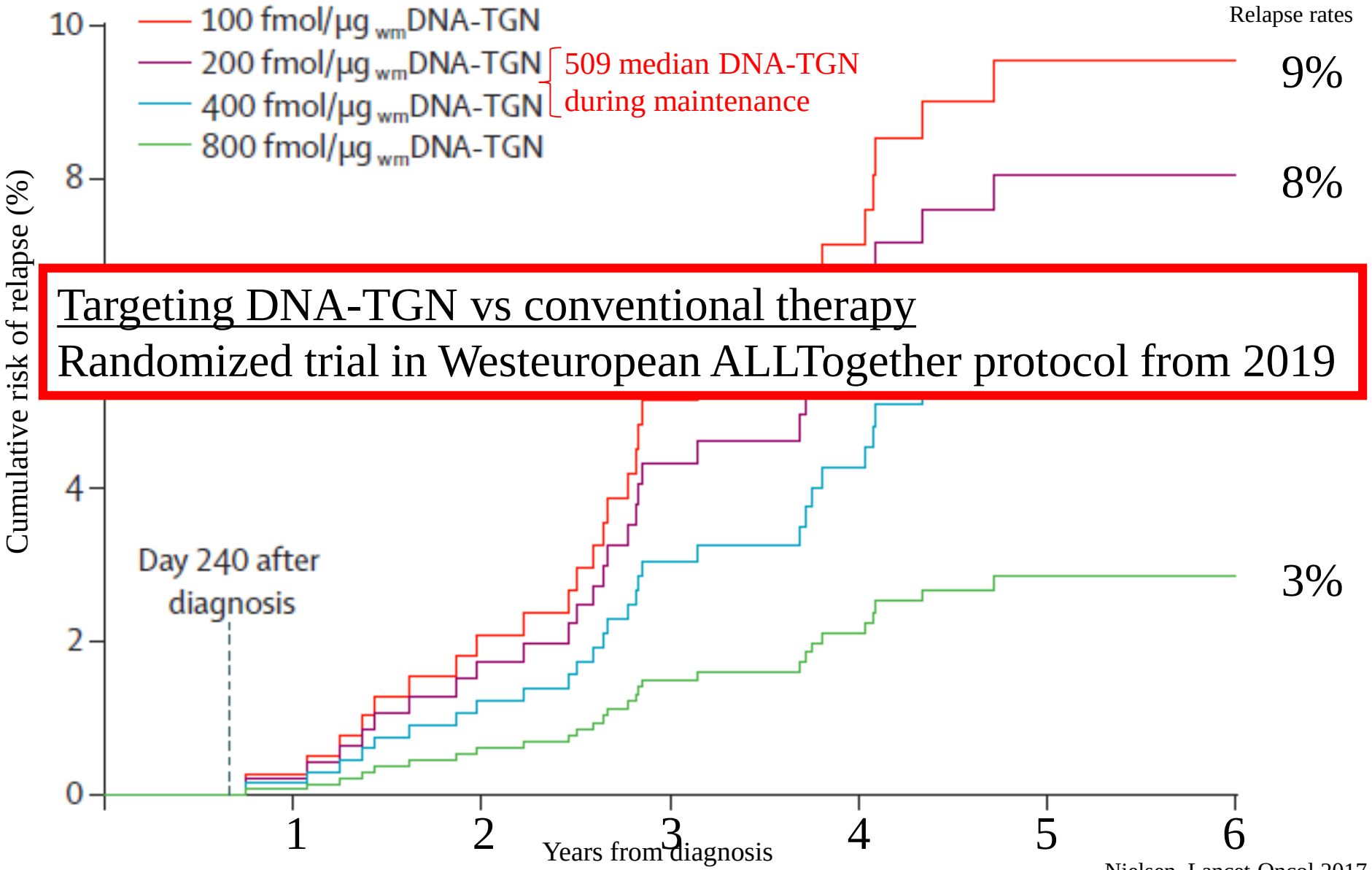
[a] Time-dependent mDNA-TGN level re-calculated at each time of event

28% reduction in relapse hazard risk per increment of DNA-TGN of 100 fmol/µg DNA

Nielsen, Lancet Oncol 2017

Simulated relapse curves for boy, 5.0 yrs, WBC 9.6 at Dx, in CR1 d240.
28 relapses in 494 day 29 MRD-positive children Min 1 DNA-TGN measurement before day 240 – then fixed

Proportional hazards model



Targeting DNA-TGN vs conventional therapy
Randomized trial in Westeuropean ALLTogether protocol from 2019

Nielsen, Lancet Oncol 2017

STAGING

Sequencing **T**umor **A**nd **G**ermline DNA –
Implications and **N**ational **G**uidelines

STAGING
Sequencing of Tumor And Germline DNA – Implications and National Guidelines

DAY 1

PEDIATRIC CANCER DIAGNOSIS

WEEK 1-2

WRITTEN MATERIAL

+

SHORT ORAL PRESENTATION

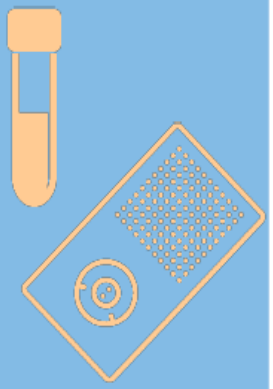
WEEK 3-4

GENETIC COUNSELING

+

DEBRIEFING

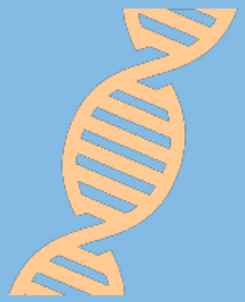
WEEK 5-6



INTERVIEW

+

BLOOD SAMPLE



WHOLE GENOME SEQUENCING

STAGING
Sequencing Tumor And Germline DNA – Implications and National Guidelines

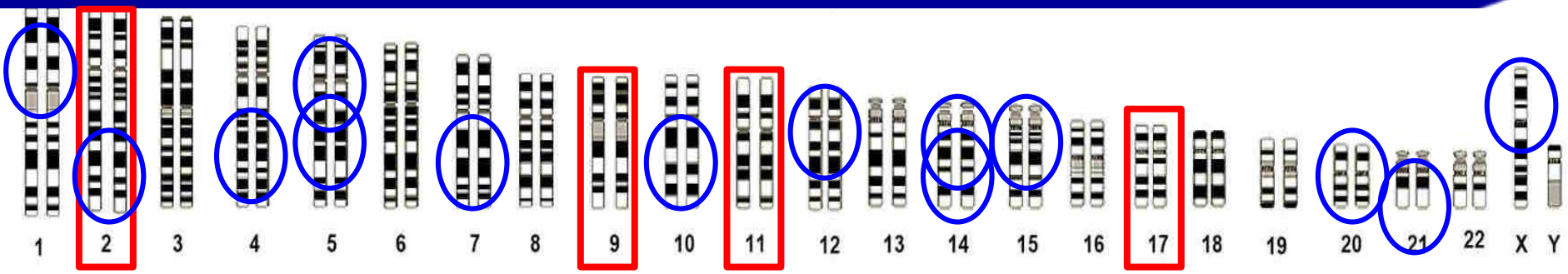
+++
STAGING – Norway

WGS/WES/tumor RNAseq ++, BCF-Sweden

Copenhagen-Lund collaboration
Copenhagen-Vilnius collaboration

The “competition” is scientific & political & financial

A look into germline DNA



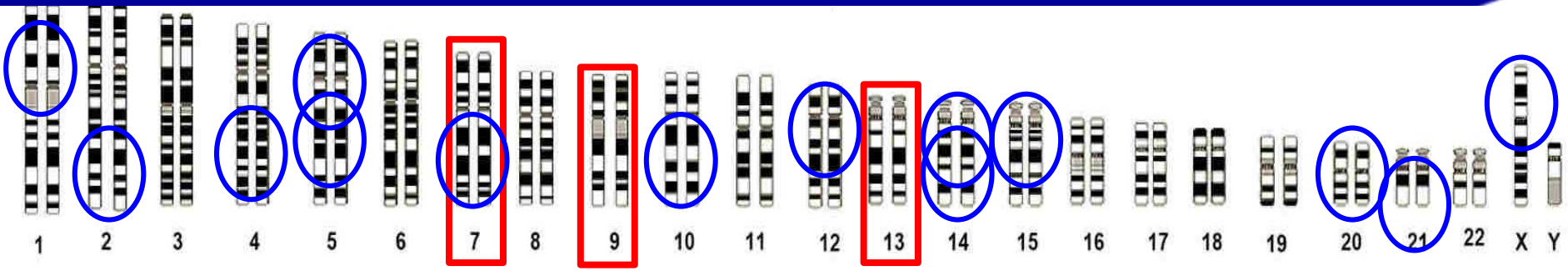
Biallel MMR mutations; ~100% absolute risk of cancer <18y

ATM mutation; ~50-100x riskof lymphoma/ALL

TP53 mutation: 90-100% life time risk of cancer, 1/3 <18y

PAX5 mutation: Markedly increased risk of ALL

A look into germline DNA

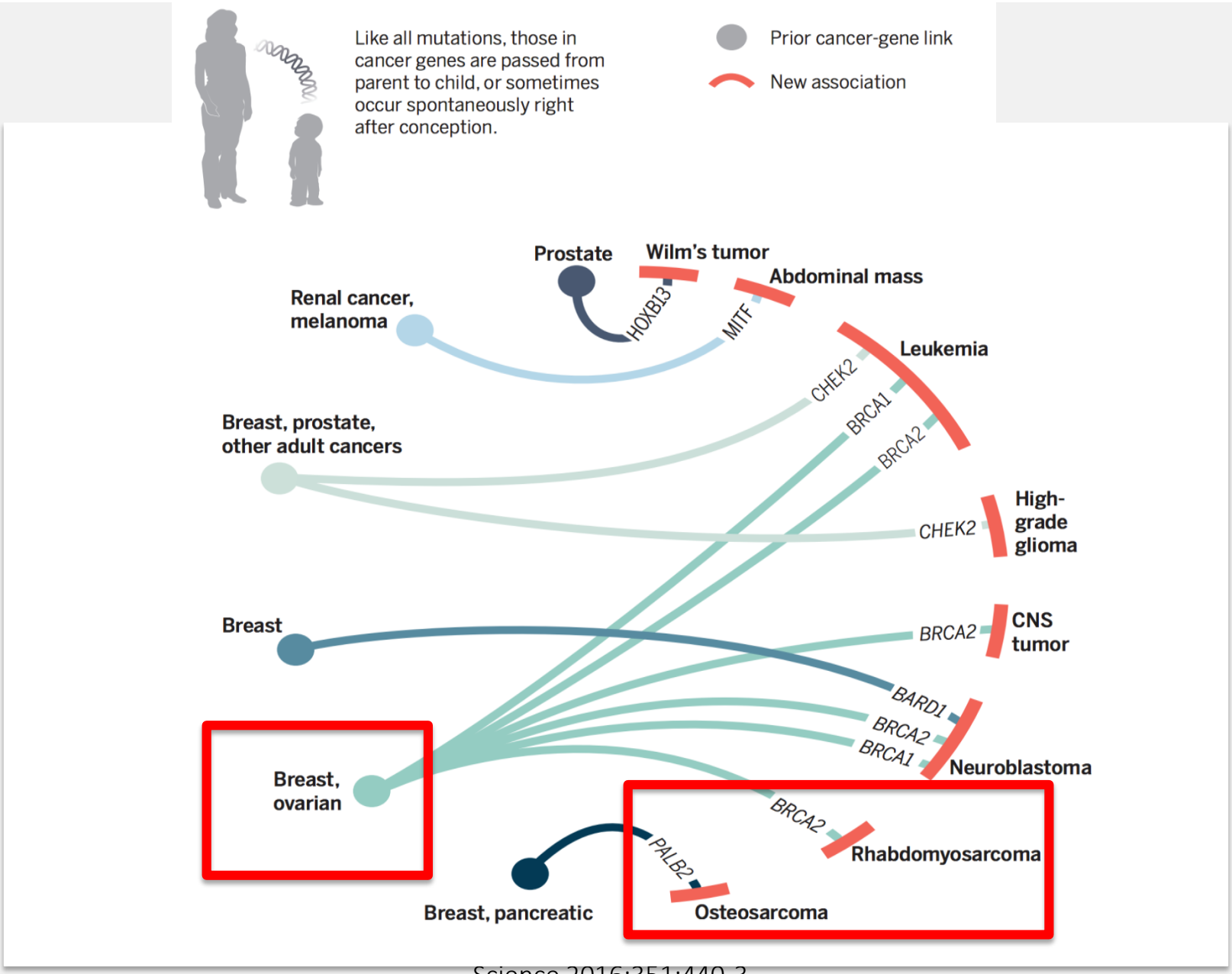


BRAF mutation; RAF inhibitors

ABL1 fusion; Imatinib

FLT3 mutation; FLT3 inhibitors

Germline mutations in adult and childhood cancer

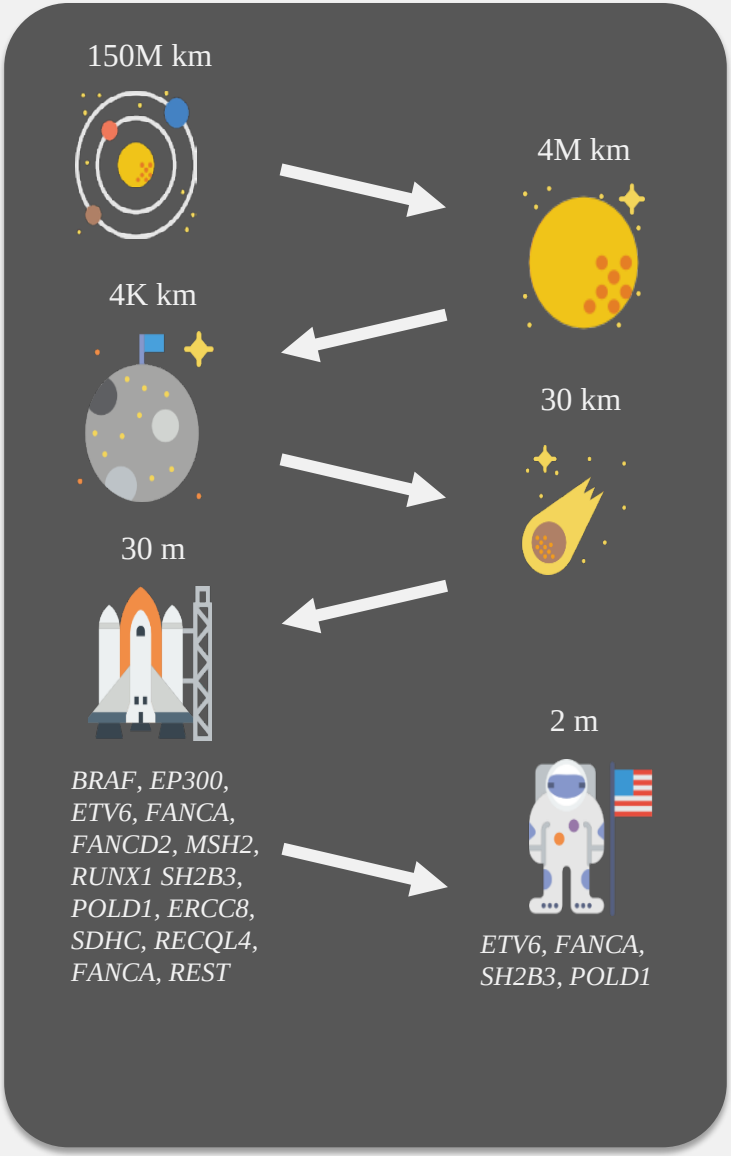


Science 2016;351:440-3

Whole genome sequencing and data analysis

100 billion bp reads
Alignment with "standard" genome
3 billion bp (genome)
Variant calling
3 million variants
In or around an exome
20.000 variants
Rare <1%
2.000 variants
216 cancer predisposition genes
20 variants
Depth, quality, impact, frequency, in silico prediction, conservation (evolution), cancer type and mutations, family history, litterature curation
0-4 variants
Multidisciplinary team conference (weekly,10-20% af alle pts)

No standards exist internationally for the bioinformatics pipeline or for reporting
Some consensus on follow-up



"Pediatric cancer families' participation in whole genome sequencing research in Denmark: parent perspectives"

STUDY FINDINGS: (15 families (30 parents), written info 2-28 days, genetic counselling 7-42 days after diagnosis)

When is the right time? Most had no objections to being approached / counselled within 4 weeks from diagnosis.

A few parents find it too early.

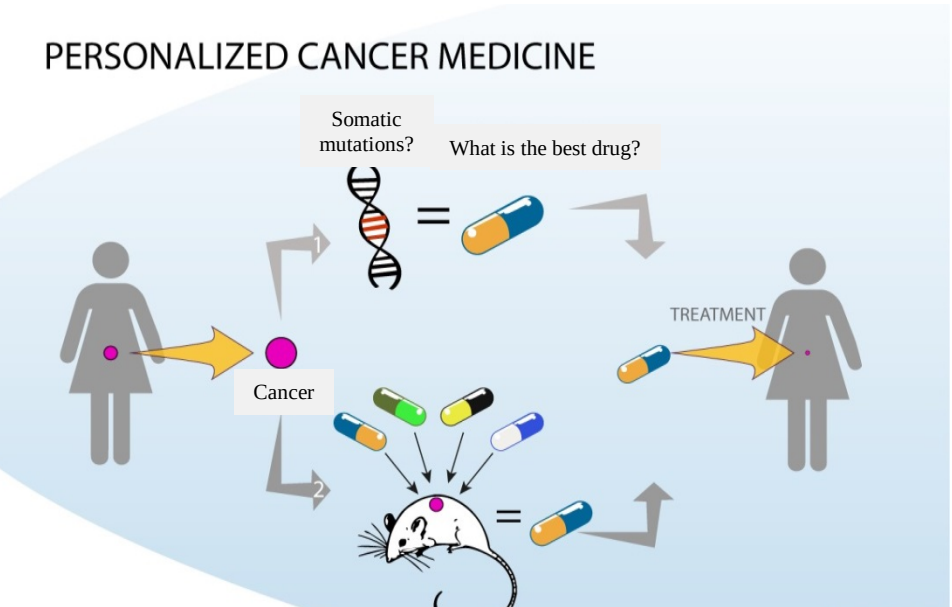
Why has this happened? Parents have many questions about cancer risk – including genetic

Making the right decision Parents have concerns regards secondary findings and expressed that they ***may*** end up regretting consent. Many families had very in-depth discussions about which findings to have reported back, at times with discordant views between parents.

Finding the genomic pieces
Personalized medicine

Patient trajectory & domains of research

Etiology	Tumor biology	Therapy	Pharmacology	Phase 1&2 therapy	Toxicities	Efficacy Cure	Late effects Rehabilitation
Host genome	Tumor genome	Tumor genome	Host genome	Tumor genome	Host genome	Tumor & host genomes	Host genome



Personalized medicine in ped. oncology:

- Cancer predisposition
- Tumor -omics (diagnosis/prognosis)
- Phase 1 & phase 2 trials
- Therapeutic drug monitoring
- Toxicities (treatment to the limit of toxicity)
- Genotype-phenotype vs phenotype-phenotype

The funding: Money and Politics

Nordic studies are especially important

- **if the Nordic group has a unique *international role***
- **if they strengthen Nordic *collaboration* – not just data provision**
  - **e.g. shared PhD-students required**
- **if a Nordic setting is needed (for study power), since the questions are unique for the Nordic *”culture”* or future Nordic *health care***